REMARKS

By the present communication, claim 1 has been amended and claims 7, 9 and 15 are canceled. Claims 10, 14, and 18-25 are withdrawn from consideration. No new matter is added. Support for the amended claim can be found throughout the application as filed, including but not limited to, original claim 7. Upon entry of the present amendment, claims 1-6, 8, 11-13, 16-17, and 26-27 will be pending and under examination. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Claim Objections

In the Office Action, claim 15 was rejected as being improper dependent form for failing to further limit the subject matter of a previous claim. Without acquiescing to the merits of the objection, claim 15 has been canceled, rendering the objection moot. Applicants request withdrawal of this objection.

II. Claim Rejections Under 35 U.S.C. § 102(b)

In the Office Action, claims 1-6, 11, 13, 15-17, 26, and 27 were rejected under 35 U.S.C. § 102(b) as being anticipated by Kainz (*Biotechniques*, 2000, 28(2):278-282, herein "Kainz"). Kainz allegedly describes the use of double-stranded DNA fragments that inhibit the activity of DNA polymerases (Office Action, p. 3). Applicants respectfully traverse the rejection.

As stated in the MPEP, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference." (MPEP 2131, *quoting Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). Kainz fails to teach each and every limitation of the instant claims. The polymerase inhibitor of claim 1 uses partially double-stranded nucleic acids. The inhibitors of Kainz are completely—not partially—double-stranded nucleic acids. Furthermore, the double-stranded fragments of Kainz are not designed to be *substantially*

incapable of extension, for example, by incorporating a base that is not recognized as a substrate for extension. Accordingly, the inhibitors of Kainz possess a different structure from the instantly claimed inhibitors. As such, the reference fails to teach all elements of claims 1-6, 11, 13, 15-17, 26, and 27. Applicants respectfully request withdrawal of the rejection.

III. Claim Rejections Under 35 U.S.C. § 103(a)

In the Office Action, claims 1-9, 11-13, 15-17, 26, and 27 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kainz, in view of Newton *et al.* (*Nucleic Acids Research*, 1993, 21(5):1155-1162, herein "Newton"). Applicants respectfully traverse the rejection.

As a preliminary matter, Applicants note that the Newton reference has been cited in the rejection, but the Office has not pointed to any specific teachings of Newton that are being used to reject the claims, nor has the Office provided any reasoning why one of ordinary skill in the art would have combined the teachings of Kainz and Newton to arrive at the claimed invention. As such, Applicants cannot comment on propriety of the rejection over the Newton reference. For at least this reason, the rejection should be withdrawn.

The Office bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Fritch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992). Furthermore, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003). In explicating the correct obviousness standard, the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (2007), reaffirmed previous holdings that an invention "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1389. The Supreme Court also confirmed that a 35 U.S.C. § 103(a) rejection based on a combination of prior art elements must still identify a reason that a person having ordinary skill in the art would combine them in manner claimed. The fact that references can be combined is insufficient to establish obviousness if one of ordinary skill in the art could not reasonably predict the result of that combination.

As stated in the previous section, Kainz fails to teach or suggest at least two elements of the claimed invention. First, Kainz does not teach incorporation of single stranded 5′ ends. The Kainz inhibitors are fully double-stranded fragments with melting temperatures determined by their respective lengths and sequences. Kainz shows a panel of nine such fragments, covering a wide range of melting temperatures. (Kainz, Table 1). The fragments were designed arbitrarily to have a specific melting temperature and are unrelated in sequence. Second, the Kainz inhibitors are not substantially incapable of being extended by a polymerase. Instead, the Kainz inhibitors use standard nucleotides for the inhibitory fragments, leaving open the possibility that they these fragments could act as primers in the amplification of non-target DNA.

In contrast, the presently claimed polymerase inhibitors are only partially double-stranded, having at least one 5′ terminal nucleotide that does not pair with the terminal 3′ nucleotide on the complementary strand. Thus, the double-stranded fragments form a partial duplex with a 5′ extension (or tail) and a 3′ end that cannot be extended by the polymerase. While the fragments are capable of binding polymerase, they are incapable of extension due to the presence of a base or blocking moiety that is not recognized as a substrate for extension. Because the polymerase cannot extend the inhibitory fragments, it remains sequestered by them until the reaction temperature rises above the melting temperature of the fragments. At that point, the polymerase is released and made available to extend any primed target sequences present in the reaction. Using this approach, a single 10-20 nucleotide oligo can be paired with a library of complementary strands truncated or offset as necessary to encompass a wide range of melting temperatures. (*See* Specification, Example 1 and Fig. 2).

The Office acknowledges that Kainz does not teach incorporation of single-stranded 3′ or 5′ ends or caps (Office Action, p. 6). However, the Office concludes that:

> Incorporation of single stranded 3′ or 5′ ends into the dsDNA fragments of Kainz as well as incorporation of a blocking moiety, is considered within the realm of routine optimization, given these elements routine to the skilled artisan and aimed at achieving the same results as the fragments of Kainz.

> Given that the polymerase of Kainz is a ds polymerase, it would have been obvious to incorporate a single-stranded portion at the 3′ or 5′ end that is not complementary to the target sequence, or to incorporate a block, as each of these are routine means of terminating polymerase extension, which is the same purpose as the terminating polymerase activity as the short dsDNA segments themselves. Therefore, one would expect for these elements to achieve inhibition of polymerase activity.

(Office Action, p. 6). Applicants respectfully disagree that incorporating a single-stranded portion at the 3′ or 5′ end or a block was a "routine means of terminating polymerase extension." The Examiner points to no evidence supporting the assertion that it is "routine" in the art to terminate polymerase extension with a single-stranded 3′ or 5′ end or incorporation of a blocking moiety. Furthermore, the Office provides no specific reason why one of ordinary skill in the art would have been modified the double-stranded DNA fragments of Kainz to include either (1) a 5′ single stranded portion or (2) a base or blocking moiety that is not recognized as a substrate for extension. The Office only states that these elements have "the same purpose as the terminating polymerase activity as the short dsDNA segments themselves." (Office Action, p. 6). However, the fact that these elements allegedly have the "same purpose" does not indicate why one would have modified the inhibitors of Kainz to be substantially incapable of extension and to have a 5′ single-stranded overhang structure.

Kainz emphasizes the importance that the inhibitors are not sequence specific and are solely dependent on the melting temperature of the fragments (*See* abstract). Kainz states:

> The sequences of the double-stranded DNA fragments used have been designed arbitrarily, starting from a pre-determined length and modified only to the extent necessary to prevent hairpins and dimer formations (according to OLIGO), but not selected in any other way.

(Kainz, p. 278, right column, second paragraph, emphasis added). The modification proposed by the Office would change the principle of operation of Kainz's inhibitors because the modified inhibitors would no longer be solely dependent on the melting temperature of the fragments for

the inhibitory function. Accordingly, there is no reason or motivation for modifying the inhibitors of Kainz that would lead one to the claimed invention with a reasonable expectation of success.

The cited references fail to teach or suggest all elements of the claims. The Office has also failed to provide a legally sufficient reason to modify the inhibitors of Kainz to be substantially incapable of extension and to include a 5′ single stranded portion. For at least these reasons, a *prima facie* case of obviousness cannot be established. Applicants respectfully request that this rejection be withdrawn.

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Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date April 16, 2010

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